

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 November 2001 (29.11.2001)

PCT

(10) International Publication Number
WO 01/90226 A1

(51) International Patent Classification⁷: C08J 3/24, 3/14, 3/16, A61K 9/51, B01J 13/04, 13/18, B22F 9/16

(21) International Application Number: PCT/CA01/00757

(22) International Filing Date: 28 May 2001 (28.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,309,575 26 May 2000 (26.05.2000) CA

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

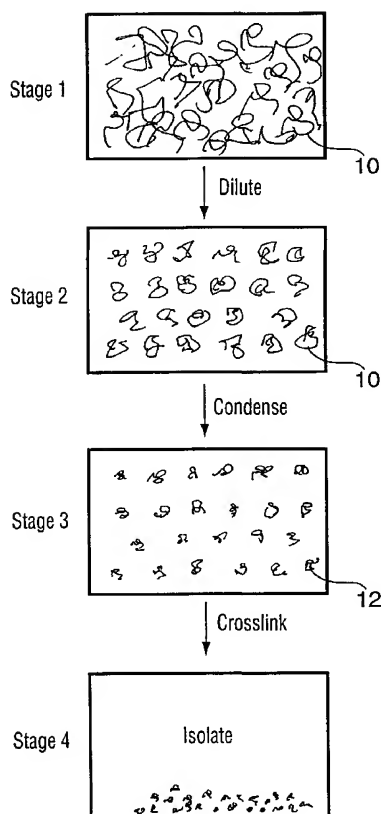
Published:

— with international search report

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CROSS-LINKED POLYMERIC NANOPARTICLES AND METAL NANOPARTICLES DERIVED THEREFROM



(57) Abstract: There are provided internally cross-linked, stable polymeric materials, in the form of substantially spherical particles, each particle consisting essentially of a single macromolecule. They have the unusual property of being soluble or dispersible in a liquid medium without significantly increasing the viscosity of the medium, rendering them potentially useful in imaging applications such as ink jet printers. They can be prepared by dissolving polymeric material in a solvent system to form a solution of the polymeric material at a concentration therein of less than the critical concentration for the polymer, causing the polymeric material to contract into an approximately spheroidal conformation in solution, cross-linking the polymeric material in solution in said spheroidal conformation so assumed, and recovering stable, cross-linked approximately spheroidal polymeric particles from the solution.



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CROSS-LINKED POLYMERIC NANOPARTICLES AND METAL NANOPARTICLES DERIVED THEREFROM

Field of the Invention

5 This invention relates to polymers, and methods for producing polymers of novel structure. More particularly, it relates to a process for cross-linking polymers to produce cross-linked polymers stabilized into particularly useful, dense structures. It also relates to novel polymeric materials having unusual properties.

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Background of the Invention

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It is known that cross-linking of polymers substantially alters the physical properties of the polymers. Cross-linking can change a thermoplastic polymer to a thermoset polymer, can alter its solubility, density and other physical characteristics. Normally, cross-linking of a polymer is an irreversible process, so that the shape, configuration and density of a cross-linked polymer remain substantially permanent once the cross-linking process is complete.

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A variety of different methods of polymer cross-linking are known. One method is reaction with chemical cross-linking reagents. This is particularly applicable where the starting polymer is unsaturated (polybutadiene, polyisoprene, styrene-butadiene copolymers, EPDM etc.), so that the groups of unsaturation take part in the cross-linking. Other methods involve creation of reactive sites such as free radicals on the polymer chains, e.g. by hydrogen abstraction using a free radical-generating initiator, by irradiation with γ -rays, X-rays, etc. Cross-linking can take place with the polymer in solution in a suitable solvent, in suspension or in bulk. Cross-linking is normally a random process, which may involve links between different polymer chains and links between points on the same polymer chain, and permits only limited control over its course and extent. In solution and suspension, non-cross-linked polymers tend to adopt an extended, coiled conformation, which is altered in a generally uncontrollable manner during cross-linking. There is a need for stable, solid particulate polymers of

predetermined shape, size and density, for use for example in ink-jet printers, photocopiers and other imaging applications, where the achievement of fine definition and resolution of images depends upon the particle size and uniformity of the particles comprising the imaging medium, and on the viscosity of the
5 imaging medium.

Summary of the Invention

The present invention provides a process whereby polymers in
10 solution are diluted so as effectively to disentangle and isolate the individual macromolecules from one another in the solution, and then caused to contract from the normal, random coil conformation to adopt an approximately spheroidal configuration. Then the macromolecules are stabilized in this conformation, e.g. by applying cross-linking conditions to the solution, so that the dissolved polymer
15 is internally stabilized in its newly assumed, spheroidal configuration, to form independent particles stabilized in that conformation. In essence, the particles are single macromolecules, independent of other, surrounding macromolecules.

By means of the present invention, dense, spherical particles of
20 polymers can be made, having a high degree of uniformity as to particle size, shape and density. The particle size is largely a function of molecular weight of the polymer, a parameter which is controllable by known methods, during polymerization. Polymers of very narrow molecular weight distribution can be made by known methods of polymerization, and these will lead to stabilized
25 polymer particles of substantially uniform particle size, following the method of the present invention. A solution of the polymer is first prepared using a solvent or mixture of solvents in which the polymer fully dissolves, and at a concentration below the critical concentration, and caused to contract into a spheroidal conformation. Then the polymer is stabilized, e.g. by cross-linking. Polymer
30 particles of very small size, average diameter in the range 0.1 - 10 nanometers (nanoparticles), can be made in this way.

The resulting polymeric materials are internally cross-linked macromolecules, i.e. substantially all of the cross-links are between groups on the same polymer chain as opposed to cross-links between groups on different polymer chains to bond the polymer chains together in a network. These internally cross-linked polymers according to the invention have solution properties which are quite different from those of the same polymeric material either before cross-linking or after cross-linking in bulk. Conventional high molecular weight polymers (100,000 and higher) have high viscosity in solution, resulting at least in part from entanglement of and interaction between individual macromolecules. If such a polymer is cross-linked in the bulk phase, the resulting polymer will not dissolve in any solvent, but may swell when contacted with solvents. Internally cross-linked materials of the invention, in contrast, even with molecular weights in excess of 1,000,000 can be dispersed in a wide variety of solvents and non-solvents, but scarcely affect the viscosity of the solution or dispersion at all. This remarkable property makes these new compositions of the invention of potential utility not only in imaging compositions as described above, but also in drug delivery applications.

Thus according to one aspect of the present invention, there is provided a process for preparing polymeric material in the form of stable nanoparticles having substantially spherical particulate form, which comprises:

dissolving a polymeric material in a solvent system to form a solution of the polymeric material at a concentration therein of less than the critical concentration for the polymeric material;

causing the macromolecules of said polymeric material to contract into an approximately spheroidal conformation in solution;

and stabilizing the polymeric material in solution in said spheroidal conformation so assumed by creating intra-molecular bonds.

Stable, intra-molecularly bonded, approximately spheroidal polymeric

nanoparticles can be recovered from the solution, if desired, by standard methods.

The term "intra-molecularly bonded" as used herein indicates the presence of internal cross-links or other bonds linking parts of the same macromolecule to itself, to the substantial exclusion of bonds linking different
5 macromolecules together ("inter-molecular bonds").

According to another aspect, the invention provides internally cross-linked particulate independent macromolecules having substantially spheroidal
10 particle shapes, said particles having the ability to be dispersed in a liquid medium without significantly changing the viscosity of the medium.

Brief reference to the drawings.

15 FIGURE 1 of the accompanying drawings is a digrammatic illustration of a preferred process according to the invention;

FIGURE 2 is an atomic force microscopy picture of one product of Example 1 below;

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FIGURE 3 is an atomic force microscopy picture of another product of Example 1 below;

FIGURE 4 is an atomic force microscopy picture of the product of
25 Example 3 below;

FIGURE 5 is the UV-visible spectrum of the product of Example 9 below;

30 FIGURE 6 is an electron microscope image, with an enlargement of the circled portion, of the product of Example 9 below;

FIGURE 7 is a curve showing the size distribution of the metal particles of Example 9 below; and

FIGURE 8 is Raman spectra of the polyacrylic acid particles and the polacrylic acid silver salt particles of Example 9 below.

Description of the Preferred Embodiments

The process of the present invention is applicable to a wide variety of polymeric materials, natural and synthetic. The polymeric materials can be homopolymers or copolymers of two or more monomers, including block copolymers and graft copolymers. It is necessary that the chosen polymeric material be soluble to a substantial extent in at least one solvent system, so as to enable it to adopt a contracted spheroidal conformation in solution, as described below.

The chosen polymeric material is first dissolved in an appropriate solvent system. This may be water, an organic solvent or a mixture of two or more such solvents. The polymeric material is dissolved such that, in solution individual macromolecules thereof remain distinct, separated and non-entangled with one another. This can be achieved by arranging that the concentration of polymer in solution is below the "critical concentration," which is the concentration at which the individual polymer chains in the solution interpenetrate. The separated, non-interpenetrating macromolecules in solution can be condensed e.g. by changing the solution characteristics, and stabilized by internal cross-linking, to a particle size which, assuming spherical shape, can be calculated from the molecular weight of the polymer. The ability of the macromolecules to achieve a condensed particle size largely in accordance with theoretical calculations, assuming spheroidal shape, acts as a check or test that the polymer in solution, prior to condensation and cross-linking, was indeed in the form of independent, separated, non-interpenetrated macromolecules for the initial stages of the process of the present invention. A person skilled in the art can readily conduct such calculations

from a knowledge of the chemistry and molecular weight of the polymer under consideration, and simple experiments to determine particle size after stabilization as described. Comparison of this with theoretical calculation and prediction can determine the critical concentration for the specific polymer solution.

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Either as it dissolves (for example in the case of sodium styrene sulfonate-vinyl naphthalene copolymers and similar copolymers), or by reduction of the solvent power of the solution, for example by adding to it a precipitating non-solvent, or a salt which changes the ionization conditions of the solution, the polymer is caused to condense and to contract to dense spheroidal structures. Then it is internally stabilized preferably by cross-linking, using a system which is compatible with the chosen polymer and the chosen solvent system, for example by exposure to γ -radiation. When each polymer molecule contains three or more internal cross-links, it can no longer expand to form its normal random coil configuration in solution. Instead, it retains its spheroidal confirmation, the density of which increases with the degree of cross-linking. In the case of some polymers, e.g. those having mutually reactive chemical groups such as polypeptides, stabilization may occur by reaction of these groups with one another as the polymer is caused to condense and contract, e.g. by formation of disulphide bridges, without application of a specific cross-linking step.

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A wide variety of polymers and copolymers can be used in the present invention, provided only that a suitable solvent system is available for them, and that the random coils can be condensed to denser spheroidal particles prior to cross-linking. Preferred polymers have ionic charges (polyelectrolytes) so that, in the preferred aqueous solvent systems, the macromolecules are mutually repellant and less likely to agglomerate prior to cross-linking.

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Examples of useful polymers in the present invention include polymers and copolymers derived from such monomers as styrene, vinyl naphthalene, styrene sulphonate, vinyl naphthalene sulphonate, acrylic acid, methacrylic acid, methylacrylate, acrylamide, methacrylamide, acrylates,

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methacrylates, acrylonitrile, N-loweralkyl acrylamides and the like.

One preferred embodiment of the invention involves the use of polymers having a critical solution temperature, i.e. a temperature below which they are soluble in water, and above which they are insoluble in water. Using the process of the present invention, such polymers can be dissolved in water, caused to assume a condensed, spheroidal conformation and internally cross-linked as described. They can then be used for delivery and controlled release of other organic compounds such as drugs. The drug can be dispersed in a suspension of the cross-linked polymer at a temperature above the critical solution temperature, at which the drug will be absorbed by the polymer in its collapsed-particulate form. When the temperature is reduced below the critical solution temperature, the polymer particle swells and slowly releases the drug. Polymers having critical solution temperatures include polymers of N-isopropylacrylamide (NIPAM), the critical solution temperature of which can be adjusted by copolymerization with other monomers.

Fig. 1 of the accompanying drawings diagrammatically illustrates a process according to an embodiment of the invention. At stage 1, the polymer exists in a concentrated solution, in which the macromolecule chains 10 are intertwined and interpenetrated, so that any attempt to cross-link them at this stage would cause inter-reaction between the polymer chains.

Upon dilution of the solution, stage 2, below the critical concentration, the polymer macromolecules 10 are spaced apart from one another, but still in their random coil configuration. Upon reducing the solvent power of the solvent system, e.g. by introducing a non-solvent or a salt, the macromolecules condense, stage 3, into generally spherical conformation 12, and can now be cross-linked, eg. by application of ionizing radiation, at stage 4, whereupon internal cross-linking, as opposed to inter-macromolecular cross-linking occurs, effectively locking the macromolecules into the configurations assumed in stage 3. Then the cross-linked, approximately spherical macromolecule particles can be recovered

e.g. by freeze drying, for use in applications referred to above.

When the macromolecule particles are re-dissolved e.g. in water, they have very little, if any, effect on the viscosity of the solvent (in any event less than a 10% resulting increase in the viscosity). This is due to the fact that the macromolecules do not agglomerate to any significant extent, nor do they expand or mutually interact to any significant extent. This unusual property renders the nanoparticles useful in a number of specialty applications. The nanoparticle macromolecules having critical solution temperature as described above are, for example, especially useful as drug carriers, where drugs are associated with the polymers in solution and delivered to very small veins and capillaries of the body, e.g. certain areas of the brain, which are so small that they cannot be penetrated by drug solutions of other than very low viscosity.

Whilst water is the preferred solvent for use in the present invention, other polar solvents can also be used if desired, alone or in mixtures with each other and in admixture with water. The best choice of solvent depends to a large extent on the choice of polymer. Polar solvents such as lower alkanols, ketones, amines, dimethylsulfoxide and the like are suitable alternatives to water, when working with a polymer of limited solubility in water.

Another aspect of the present invention comprises the use of internally cross-linked macromolecules as described above in the preparation of nanoparticles of metals, i.e. metal particles which are substantially spherical in shape, and which have an average diameter in the range 0.1 - 10 nanometers, preferably from 0.1 - 8 nanometers and more preferably from 0.1 - 5 nanometers.. Such nanoparticles of metals comprise another aspect of the invention. This process aspect uses internally cross-linked polymers as described above, in which the polymer is a polyelectrolyte such as polyacrylic acid or a salt thereof e.g. sodium polyacrylate. For example, by dissolving them in water containing a large excess of ferrous ions, the sodium ions can be replaced by ferrous ions. After removal of the sodium ions, the particles can be heated in air or oxygen to above

200-300°C. The polymer content is largely removed by pyrolysis, leaving extremely small particles of iron oxide with very large surface area and important electrical and catalytic properties. If the process is carried out in a reducing atmosphere, high surface metal particles can be obtained. Other metal salts such as silver salts (silver nitrate for example), copper salts and gold salts can be used to produce finely divided metal particles useful in imaging and, because of their very high surface area, in catalysis. Palladium, platinum, titanium and molybdenum are examples of metals which can be prepared in nanoparticle form according to the present invention, for use in catalysis. Substantially any metal which is stable in its metallic form and which has a water soluble salt can be used in this way. The metal salt can be dialyzed against the sodium polyacrylate (or similar polymeric salt) particles of the invention, to remove the alkali metal and replace it with the other metal. Then the product is reduced, e.g. by application of laser radiation, and solid metal nanoparticles e.g. silver particles, in some cases surrounded by a fine layer of residual polymer which has a stabilizing effect, are obtained.

In another modification, ionic groups on internally cross-linked polymers of the present invention, for example the sodium acrylate groups in the particles made in examples 1, 2 and 8 below, can easily be converted to other useful functional groups. Sodium acrylate groups for example can be converted converted to the corresponding acid chloride by treatment with thionyl chloride. Dye molecules containing reactive hydroxyl or amino groups can then be permanently bound to both the surface and the interior of the particles giving rise to products useful in imaging applications such as in ink-jet printing.

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The invention is further described with reference to the following specific illustrative examples.

Example 1 - Internally Cross-linked Polyacrylic Acid

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The sodium salt of poly(acrylic) acid (Polysciences Inc. Cat #18755), of molecular weight of 1,300,000, was used in a cross-linking process according

to the invention. 97 mg of polymer was dissolved in 100ml of distilled water. After solution was complete the pH was 8.2, and 98mg of sodium chloride was slowly added to cause the polymer particles to contract. 5cc. of the solution was flushed with nitrogen, sealed in a glass vial, and irradiated with 10 megarad of Co⁶⁰ γ radiation. After radiation the vial was opened and the solution dialysed against water for 5 days to remove the salt, and the polymer particles recovered by freeze drying under vacuum. The particles were studied by atomic force microscopy (A.F.M) (film cast onto mica, to produce tapping mode AFM height image) and shown to be perfectly spherical, with diameters of 6 to 10 nanometers (see Fig. 2). No such particles were observed in the uncross-linked control sample. The particles observed are close to the size calculated for a completely collapsed macromolecular chain of molecular weight one million. When dispersed in water at a concentration of 1%, the solution had a viscosity virtually the same as pure water. At the same concentration a water solution of uncross-linked starting material was much more viscous.

The procedure was repeated with a polyacrylic acid (sodium salt) of molecular weight about 700,000, and the A.F.M. picture of this product is presented as Fig. 3 hereto. The spherical shape of the particles is clearly apparent from this picture. The scale on the Figure is in millimicrons. The particles have a diameter of approximately 4 nanometers (0.4 millimicrons).

Example 2

The procedure of Example 1 was repeated except that before addition of the sodium chloride the pH of the solution was reduced to 3.2 by addition of small amounts of 0.1 N hydrochloric acid. After addition of sodium chloride and cross-linking with 10 megarad of γ -rays, nanoparticles of the same size (6-10 nanometers) were observed as in Example 1 by A.F.M.

Example 3

Copolymers of sodium styrene sulfonate and vinyl naphthalene containing about equal quantities of each comonomer are known to form hypercoiled pseudomicellar conformations in water, i.e. they do not form expanded random coils, but are collapsed into much smaller spherical structures with much higher coil density due to the hydrophobic interactions between the naphthalene groups and water. These particles are negatively charged due to the ionization of the styrene sulfonate groups in water. The polymers can also be internally cross-linked by the following procedure. A polymer containing 50% by weight sodium styrene sulfonate and 50% of vinyl naphthalene was prepared in benzene solution AIBN as catalyst. After isolation and purification by dialysis against pure water it had a molecular weight M_w of 200,000.

100 mg of this polymer was dissolved in 100 ml distilled water and after purging with oxygen-free nitrogen was irradiated with a dose of .40 megarad of Cobalt⁶⁰ γ -rays. A.F.M. analysis of the resulting particles showed spherical particles with an average diameter of 7.5 nanometers. The A.F.M. picture of the particles is presented as Fig. 4 hereof. A 1% solution of these particles in water showed very little increase over that of water itself.

20 **Example 4**

Internal cross-linking can be carried out by other means besides γ radiation. In some cases, irradiation of the aqueous dispersion with high intensity U.V. laser light will cause internal cross-linking. A simpler procedure is to prepare a copolymer with a small number of double bonds which can be connected by vinyl polymerization. In this example a copolymer of 50% styrene sulfonate and 48% vinyl naphthalene and 2% divinyl benzene was prepared as in Example 3. 100 mg of this polymer was dissolved in 100 ml of water to which was slowly added with stirring 1.0 cc of benzene containing 4 mg styrene and 1 mg of AIBN (azobis-isobutyryl nitrile). After purging with nitrogen 2 cc of this mixture was heated to 70°C for 5 hours with stirring. After isolation and purification by dialysis spherical nanoparticles were observed by A.F.M.

Example 5

An additional 2 cc of the solution prepared in Example 4 was shaken with a small amount of styrene monomer and allowed to separate. Excess styrene was removed and the polymer was internally cross-linked by exposure of the solution to near ultraviolet light ($\lambda = 313$ nm from the American Ultraviolet Irradiation System for 1 hour. After isolation and purification cross-linked nanoparticles with the viscosity properties of the γ irradiated materials from Example 1 and 2 were produced.

Example 6

Poly N-isopropyl acrylamide (NIPAM) is an important polymer which is often used in drug delivery systems. It has a lower critical solution temperature (LCST) of 31°C. It is soluble in water below this temperature but precipitates sharply above this. This temperature can be lowered by copolymerization with hydrophobic monomers such as acrylonitrile and raised by hydrophilic monomers such as acrylamide. These co-polymers can be internally cross-linked by any of the procedures described above. In a specific example 100 mg of polyNIPAM with a molecular weight of 200,000 g/mole was dissolved in 100 ml water at 20°C and was cross-linked with 10 megarads of γ radiation. After isolation and purification, the internally cross-linked 5-10 nm nanoparticles can be used for the controlled delivery of other organic compounds. For example the drug can be absorbed by the collapsed particle in a water dispersion above LCST. After removal of the unabsorbed drug, the dispersion will remain stable until the temperature of the water is reduced below LCST, at which point the particle swells and slowly releases the drug. Since the size of the internally cross-linked nanoparticle is extremely small (~10 nm) it can access almost any part of the human body including the smallest blood capillaries which makes it of interest in a variety of medical therapies. The delivery polymers can also be made sensitive to pH instead of temperature.

Example 7

Polymers such as NIPAM, polyacrylamide and polyethylene oxide, which do not contain ionized groups, are difficult to keep separate in water solution while the cross-linking process is taking place. This reduces the yield and purify of the desired internally cross-linked nanoparticles. Cleaner products and higher conversions can be achieved by including an ionizable comonomer. A copolymer of 2% acrylic acid and 98% NIPAM was prepared. At a pH of about 8-9 in water most of the acrylic acid units will be ionized, thus giving a strong negative charge to each polymer molecule. At high dilution, this prevents the agglomeration of individual chains to form larger particles. 100 mg of this polymer was internally cross-linked by the procedure of Example 6. A.F.M. studies of the internally cross-linked particles showed a much lower concentration of larger agglomerated particles than those prepared in Example 6.

Example 8

A solution of sodium polyacrylate was prepared as in Example 1, and after the addition of sodium chloride, 4 mg of 4,4'-diazidostilbene-2,2' sodium sulfite dissolved in 1 cc benzene was added slowly with continuous stirring. After flushing with nitrogen, the ampoule was sealed and irradiated for 1 hour with 313 nm U.V. light in the American Ultraviolet Irradiation system. After irradiation the product was isolated by freeze drying and purified by dialysis as in Example 1. A.F.M. measurements showed particles similar to those found in Example 1.

Example 9 - nanoparticles of metal.

Nanoparticles of polyacrylic acid sodium salt prepared according to Example 1 were dialysed against dilute hydrochloric acid to remove the sodium ions, and then treated with excess silver nitrate in aqueous solution to form the silver salt of the acrylic acid groups in the polymer particles. Irradiation of these particles in aqueous dispersion with γ -radiation (10 Mrad) gave a dark orange

solution. The UV-visible spectrum shown in Fig. 5 shows peaks corresponding to the well-known surface plasmon of silver colloids of size smaller than the wavelength of light, indicating that the silver ions have been reduced to metallic silver. The silver colloids are much more stable than those reported in the literature, as indicated by the fact that the plasmon band intensity did not change for many weeks after preparation.

After isolation of the particles and drying of them, spherical particles of diameter about 5 nm were observed by AFM. An electron microscope examination (TEM), Fig. 6, shows that the spherical silver particles are surrounded by a hazy region believed to be unreacted polymer, a possible factor in the enhanced stability of the silver nanoparticles.

The average diameter of the reduced silver particles was 3.5 ± 0.53 nm. The diameter of the exterior, including the hazy region, was 5.2 ± 0.8 nm. The particle size distribution is shown on Fig. 7.

Similar results were obtained by irradiation of the original salt particles with an intense laser pulse from a picosecond quadrupled Nd:YAG laser or XeF excimer laser, and by a chemical reducing agent such as sodium in liquid ammonia.

Similar experiments with iron and copper salts gave similar results, with aqueous solutions giving rise to various colours, depending upon the size of the particles.

Further evidence of encapsulated particles is shown on Fig. 8, Raman spectra, showing the surface enhanced Raman effect of silver nanoparticles on poly acrylic acid, PAA. In the absence of the reduced metal, the Raman peaks for pure polyacrylic acid are hardly discernible, but after the silver salt is reduced to metallic silver, strong enhanced Raman peaks are observable. This is strong evidence for the encapsulation of the silver particles by the

remaining polymer from the original particle. This coating can be easily removed by washing with a suitable solvent, or by heating to 300°C or higher in a reducing atmosphere.

5 **Example 10- Larger particles.**

Larger particles of polyacrylic acid salts and other polymers for the preparation of metal particles by the process of the invention can be made by emulsion polymerization in the absence of surfactant, by the method of
10 O'Callaghan et.al, Journal of Applied Plymer Science, Vol 58, 2047-2055 (1995). This paper describes a method of making monodisperse polymer latices with sizes of 40 nm and higher.

By following the procedure of this paper, there was prepared a
15 copolymer of butyl acrylate (30%) with acrylic acid (70%), cross-linked with 3% divinylbenzene. The average size of these particles was 230±20 nm. Treatment with silver nitrate as in Example 9 followed by laser irradiation with the Nd:YAG laser while stirring the aqueous dispersion gave silver containing nanoparticles about 200 nm in diameter.

CLAIMS:

1. A method for preparing polymeric material in the form of stable, substantially spherically nanoparticles, comprising the steps of:

5 (a) dissolving a polymeric material in a solvent system to form a solution of the polymeric material at a concentration therein of less than the critical concentration for said polymeric material;

(b) causing the molecules of said polymeric material to contract into dense particles in solution of approximately spherical conformation; and

10 (c) chemically stabilizing said particles in said spherical conformation so assumed.

2. A method according to claim 1, wherein the chemical stabilization of said particles results from internal, cross-linking of the molecules of said polymeric material, following their contraction, into particles of approximately spherical conformation in solution.

3. A method according to claim 2, wherein step (b) is effected by reducing the solvent power of the solvent system for said polymeric material, so that the molecules thereof condense and contract, forming said dense particles.

4. A method according to claim 2 or claim 3, wherein said polymeric material is a polymer or a copolymer derived from monomers selected from the group consisting of styrene, vinyl naphthalene, styrene sulfonate, vinyl naphthalene sulfonate, acrylic acid, methacrylic acid, methylacrylate, acrylamide, methacrylamide, acrylates, methacrylates, acrylonitrile and N-loweralkyl acrylamides.

5. A method according to claim 3, wherein said polymeric material exhibits a critical solution temperature in said solvent system, and said solvent power is reduced by lowering the temperature of the solution from above to below the critical solution temperature.

6. A method according to claim 5, wherein said solvent system is aqueous and said polymeric material is a polymer or copolymer of N-isopropyl acrylamide.

5 7. A method according to claim 3, wherein said solvent power is reduced by adding a non-solvent to said solvent system.

8. A method according to claim 3, wherein said solvent system comprises a polar solvent, said polymeric material forms polyionic macromolecules in solution, and the solvent power is reduced by adding a salt to the solution.
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9. A method according to claim 8, wherein said polar solvent is water and said polymeric material is the sodium salt of poly(acrylic) acid.

10. A method according to claim 9, wherein said salt is sodium chloride.
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11. A method according to claim 2, wherein said solvent system in water and said polymeric material spontaneously forms hypercoiled, pseudomicellar conformations in aqueous solution, step (b) being effected by and simultaneous with step (a) of the method.
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12. A method according to claim 11, wherein said polymeric material is a copolymer of sodium styrene sulfonate and vinyl naphthalene.

13. A method according to any one of claims 2 to 12, wherein said internal cross-linking is effected by exposing the solution, following step (b), to gamma-radiation.
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14. A method according to any one of claim claims 2 to 12, wherein said internal cross-linking is effected by exposing the solution, following step (b), to ultraviolet radiation.
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15. A method for preparing a polymeric material in the form of stable,

substantially spherical nanoparticles, comprising preparing a solution of polymeric material according to the method of any one of claims 1 to 14, then recovering stable, substantially spherical polymeric nanoparticles from the solution.

5 16. A method according to claim 15, wherein recovery of said polymeric nanoparticles is effected by freeze drying of said solution.

17. A method for preparing nanoparticles of a metal, comprising the steps of:

10 (i) preparing a solution of the sodium salt of poly(acrylic) acid in the form of stable, substantially spherical nanoparticles, by the method of claim 9 or claim 10;

 (ii) removing spherical nanoparticles of the polymeric material from the solution;

15 (iii) exposing the nanoparticles of polymeric material to an excess of a salt of said aqueous solution to form the acrylic acid salt of the metal within the nanoparticles of acrylic polymeric materials; and

 (iv) effecting the reduction of said metal salt to produce spherical nanoparticles of the metal.

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18. A method according to claim 17, further comprising the removal of residual polymeric material from said nanoparticles of metal.

25 19. A method according to claim 17 or claim 18, wherein said metal is selected from the group consisting of gold, silver, copper and iron.

20. Substantially spherical particles of a metal having an average diameter in the range of 0.1 to 10 nanometers.

30 21. Particles according to claim 20 wherein the metal is selected from gold, copper, silver and iron.

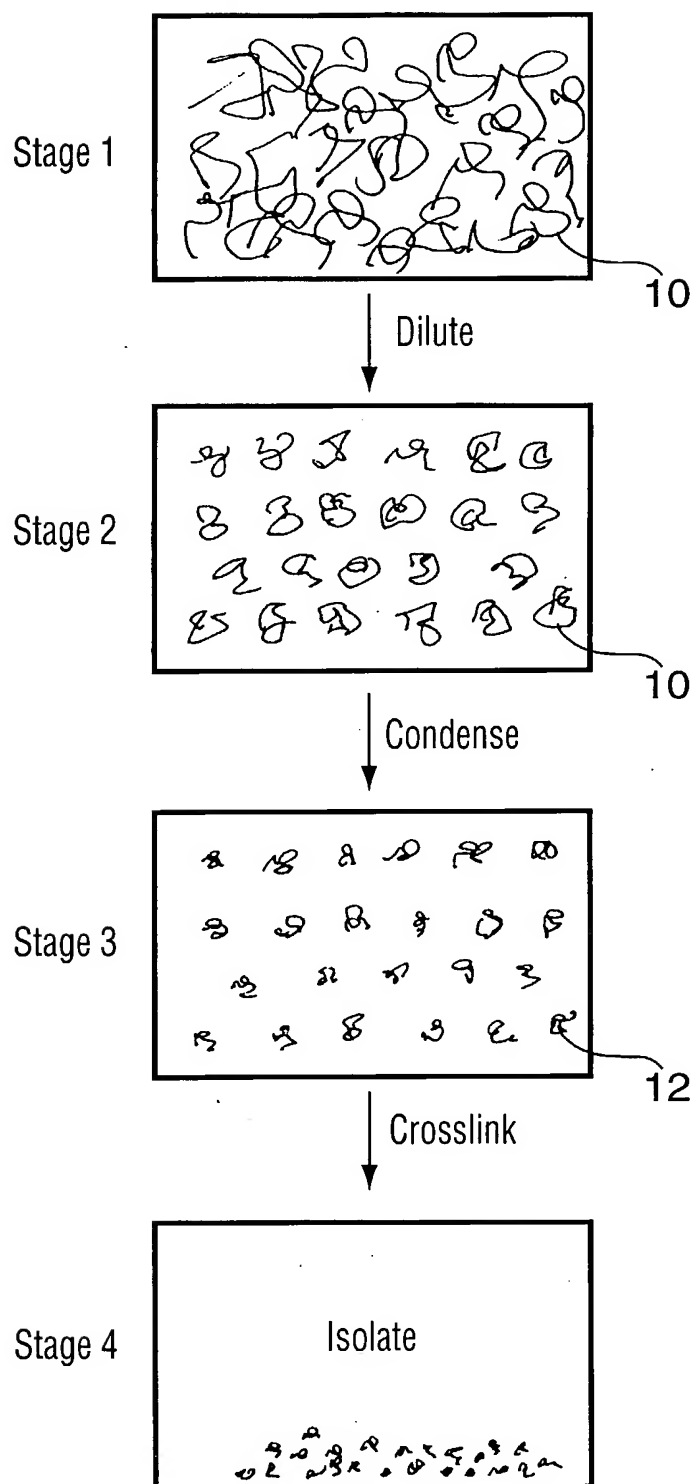
22. Particles according to claim 20 or claim 21 having an average diameter in the range of 0.1 to 8 nanometers.

5 23. Internally cross-linked, particulate, independent macromolecules having substantially spheroidal particle shapes, said particles having the ability to be dispersed in a liquid medium without significantly changing the viscosity of the medium.

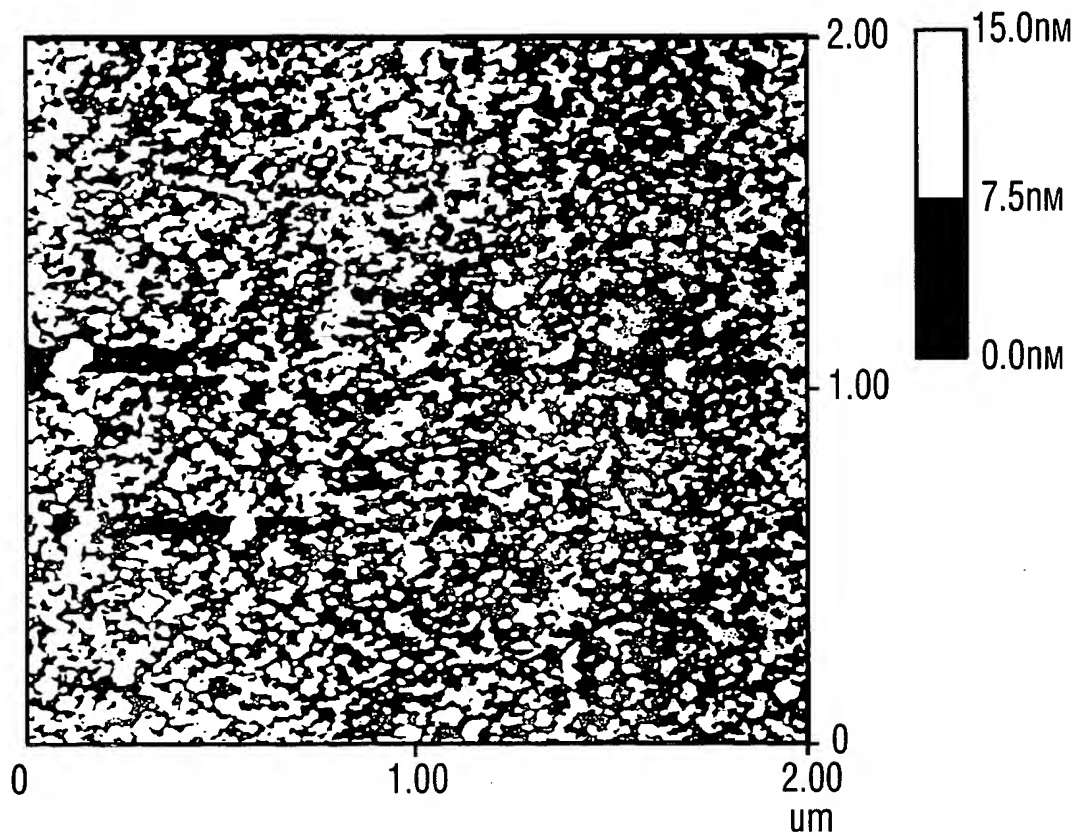
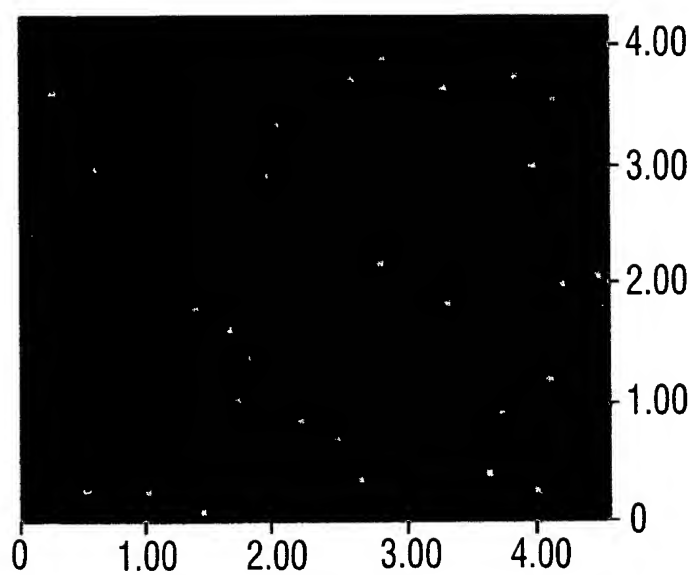
10 24. Macromolecular particles according to claim 23 o average diameter 0.1 - 10 nanometers.

25. Macromolecular particles according to claim 23 or claim 24 comprising a polyelectrolyte.

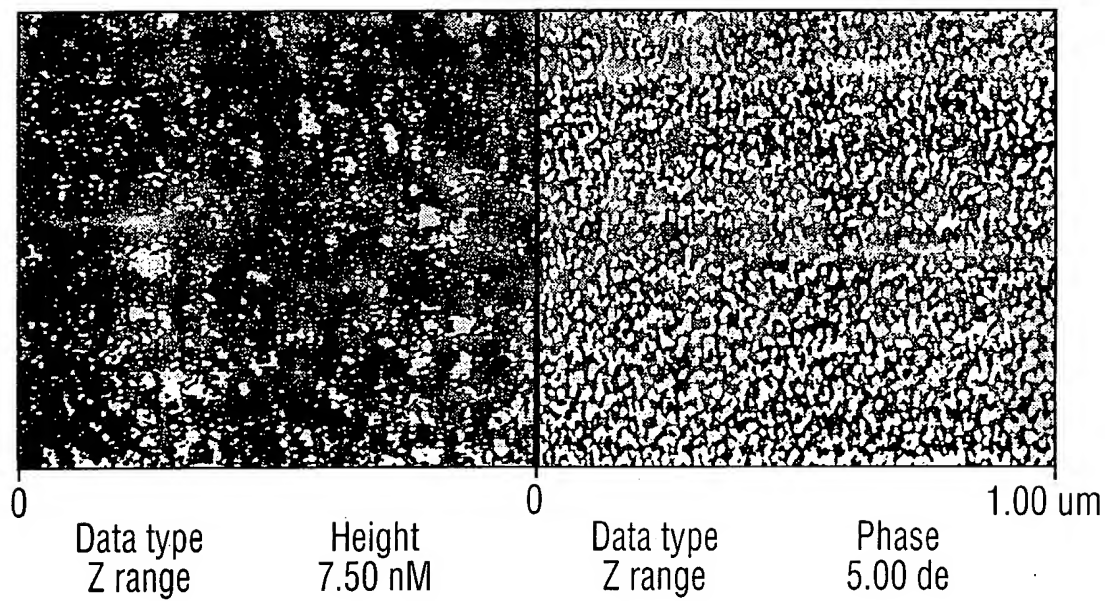
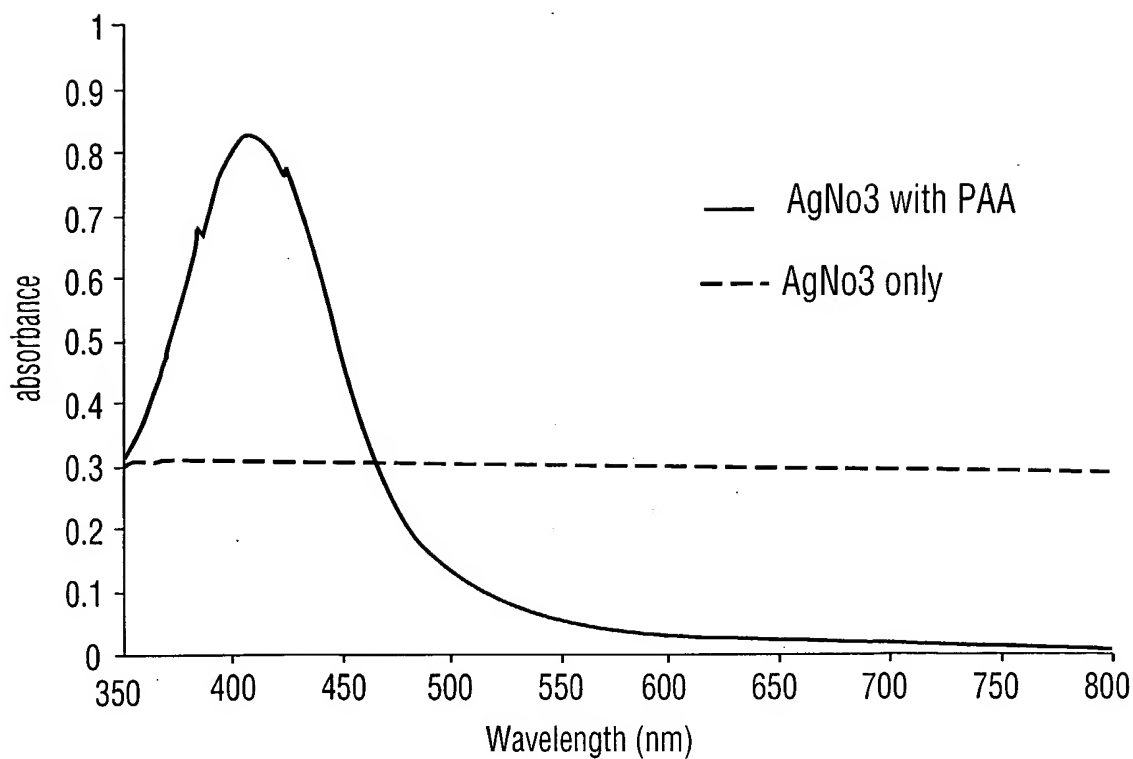
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**FIG. 1**

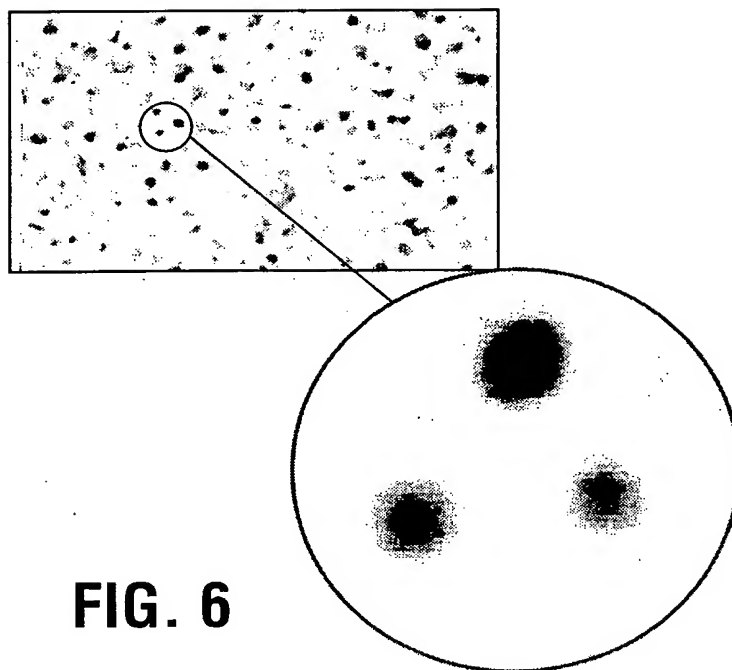
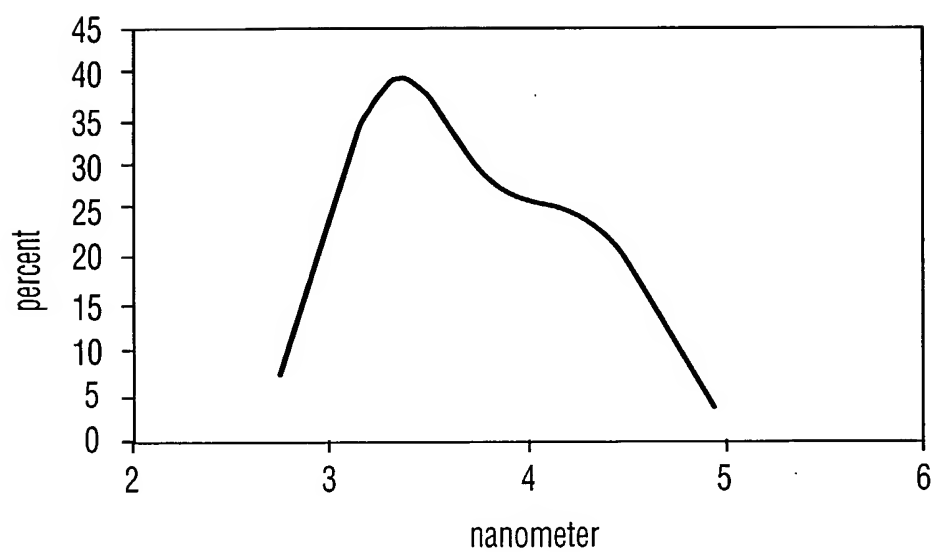
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**FIG. 2****FIG. 3**

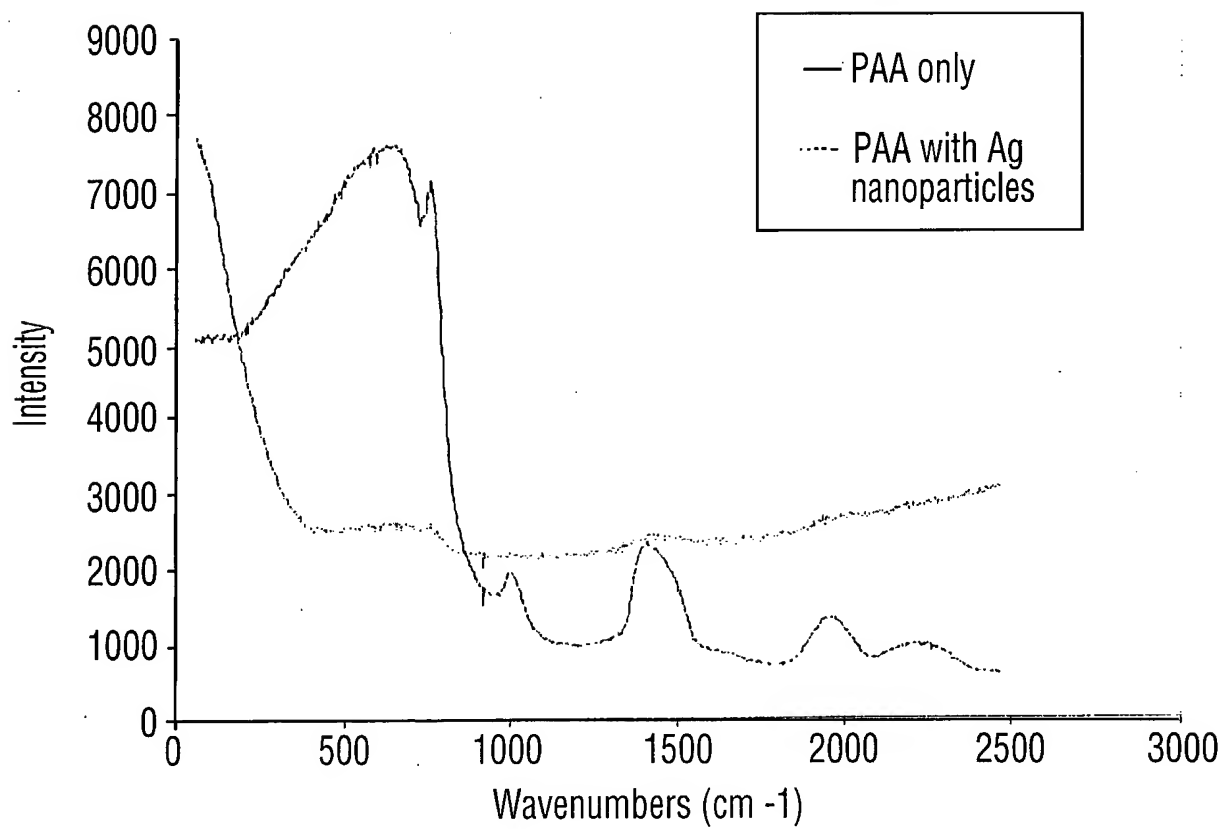
3/5

**FIG. 4****FIG. 5**

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**FIG. 6****FIG. 7**

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**FIG.8**

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00757

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08J3/24 C08J3/14 C08J3/16 A61K9/51 B01J13/04
B01J13/18 B22F9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08J A61K B01J B22F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

9 August 2001

Date of mailing of the international search report

17/08/2001

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